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EXAMINER	
KERR,K	
ART UNIT	**PAPER NUMBER**
1652	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/471,349	Applicant(s) Sahni et al.
	Examiner Kathleen Kerr	Group Art Unit 1652

☒ Responsive to communication(s) filed on *1/26/01*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-32* is/are pending in the application.

Of the above, claim(s) *4-31* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3 and 32* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Application Status

1. The instant action is in response to Applicants' election (Paper No. 10) which was in response to a written restriction requirement (Paper No. 8). Claims 1-32 are pending in the instant application.

Election

2. Applicants' election without traverse of Group I, Claims 1-3 and 32, in Paper No. 10 is acknowledged. Claims 4-31 are withdrawn from consideration as non-elected inventions. Claims 1-3 and 32 will be examined in the instant Office action.

Priority

3. Applicants are granted the benefit of priority for the foreign application 3825/DEL/98 filed in India on December 24, 1998 as requested in the declaration; the certified copy of said foreign application has been received in the instant application.. The priority date granted for purposes of prior art in this Office action is December 24, 1998.

Information Disclosure Statement

4. The information disclosure statement (Paper No. 6) filed June 26, 2000 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Drawings

5. The drawings are considered informal for the reasons detailed in the attached copy of PTO Form 948. Appropriate correction is required prior to allowance.

Sequence Compliance

6. Previously in prosecution, Applicants were required to comply with the sequence rules in a Notice to Comply (Paper No. 5). In response, Applicants submitted a sequence amendment (Paper No. 7) which has been entered and which supplied the necessary sequence listing in computer readable form and paper copy, as well as a statement of their sameness.

Despite Applicants' sequence amendment, this application fails to *fully* comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).

a. In the Brief Description of the Figures on pages 12-13, Figures 3 and 6 disclose DNA and amino acid sequences and Figures 11, 12, 14, 17b, 19b, 21b, and 22b disclose DNA sequence, Figure 12 discloses DNA sequences without benefit of SEQ ID NOs.

b. On pages 29, 32, 37, 38, 45, and 49, DNA primers are disclosed without benefit of SEQ ID NOs.

If these sequences are in applicant's sequence disclosure as filed, the applicant must amend the specification to identify the sequences appropriately. If these sequences are not in applicant's sequence disclosure as filed, the applicant must provide a substitute computer readable form (CRF) copy of the "Sequence Listing", a substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d).

Objections to the Specification

7. The specification is objected to because the top margin is less than 2.0 cm (3/4 inch) as required by 37 CFR 1.52 (see also MPEP 608.01). Substitute application papers with proper margins are required.

8. The title is objected to because the term "Novel" is redundant in the title of a patent. The Examiner suggests deleting the word "Novel" from the title.

9. The abstract is objected to because the first "sentence" of the abstract is not a complete sentence. Appropriate correction is required.

Objections to the Claims

10. Claim 2 is objected to for two informalities. In line 2, the subject ("streptokinase molecule") is singular while the verb ("bind") is plural. In line 2, the word pair is misspelled as "pari". Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 1, line 1, the phrase "polypeptide bond union between" is unclear. From Figure 1, it would seem Applicants intend to claim a single polypeptide chain, hybrid protein which would contain an amide bond between SK and fibrin-binding domains (FBDs) of fibronectin(FN); however, this is not clear from the claim language as filed.

Also in Claim 1, lines 4-6, the phrase "to achieve various motifs for joining the fibrin binding domains with streptokinase or its modified forms" is unclear as to what limitation this phrase places on the claimed subject matter. Since the claim limits the modified or fragments of streptokinase (SK) to those capable of plasminogen (PG) activation (first half of hybrid), it seems that this phrase intends to indicate retained function of FBDs(FN) in the claim; however, this is

not clear from the claim language. The Examiner suggests the following rewrite of Claim 1 to address these issues provided that appropriate support for the following claim language can be supported by the instant specification as originally filed:

---1. A hybrid plasminogen (PG) activator comprising a first polypeptide and a second polypeptide linked by a polypeptide amide bond as a single polypeptide chain,

wherein said first polypeptide is selected from the group consisting of

(a) streptokinase (SK),

(b) modified forms of SK capable of PG activation, and

(c) fragments of SK capable of PG activation; and

wherein said second polypeptide is selected from the group consisting of

(a) fibrin binding domains 1 and 2 of human fibronectin (FN),

(b) modified forms of fibrin binding domains 1 and 2 of human FN capable of binding fibrin,

(c) fibrin binding domains 4 and 5 of human FN, and

(d) modified forms of fibrin binding domains 4 and 5 of human FN capable of binding fibrin;

wherein the hybrid PG activator binds fibrin and activates PG after a pronounced duration, or lag, following exposure of the hybrid PG activator to a suitable animal or human PG.---

The Examiner also suggests alternative language to further clarify the amide/peptide bond issue; the use of product-by-process language, wherein the hybrid plasminogen activator is produced from the encoding DNA, would clarify any ambiguity concerning the single polypeptide chain while avoiding FBD(FN)-SK conjugate complexes found in the prior art. Moreover, Applicants are reminded that product-by-process claims are drawn to the product, and hybrid plasminogen activators, produced by chemical (not recombinant) technology, would still read on the instant claim.

12. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of fibrin binding domains 1 and 2 or 3 and 4 of human fibronectin (i.e. the residue numbers of said fragments of FN) are unclear. Appropriate definition of these fibronectin fragments is required.

13. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "pronounced" is a relative term which renders the claim indefinite. The term "pronounced" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Appropriate definition of the metes and bounds of the instant term is required.

14. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "suitable animal ... plasminogen" is unclear and confusing. The instant specification does not define those animal PGs which are suitable. Moreover, since human FN binding domains are used and these binding domain help bind the SK portion (PG activating portion) of the PG activator to fibrin, the instant PG activator seems functional (able to activate

PG) only with human PG which is bound by the fibrin binding domains used. Appropriate definition of "suitable" animal PG or deletion of the phrase is required.

15. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 32, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Moreover, the use of "such as" and "etc" is confusing. If these examples of stabilizers are identified in the instant specification, as originally filed, as such, the Examiner suggests deleting "such as ... anesthetic agents" from the claim entirely.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for hybrid plasminogen activators having modified forms of SK which are capable of PG activation, does not reasonably provide enablement for hybrid plasminogen activators having modified forms of SK which are incapable of PG activation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these

claims. The breadth to which the instant claims are drawn, i.e. hybrid plasminogen activators which contain modified SK which does not activate plasminogen, appears to be due to the confusing language of the instant claims (see above for clearer rewrite of Claim 1); however, the Examiner will present arguments below.

To make hybrid PG activators which contain modified forms of SK, which no longer activate PG, would require some other portion of the hybrid PG activator to activate PG; this would require undue experimentation. Applicants have provided no working examples or guidance to suggest the activation of PG by another portion of the hybrid PG activator. One of skill in the art would be required to produce such portions from other PG activating polypeptides. Thus, the breadth of the instant claims are not enabled by the specification.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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17. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Vogel et al. (this reference is related to IDS reference AF). The instant claims are drawn to conjugated polypeptides which activate plasminogen (PG) comprising (1) streptokinase (SK) and (2) human

fibronectin (FN) or fragments of FN, which fragments contain fibrin binding domains (FBDs) 1 and 2 or 4 and 5. The instant rejection is due to the lack of clarity in Claim 1 concerning the "polypeptide bond union" (so Claim 1 can read on conjugated polypeptide complexes), the relative term "pronounced" (so any lag limitation is removed from Claim 1), and the metes and bounds of FBD domains 1 and 2 or 4 and 5 (see above concerning all 112, second paragraph rejections).

Vogel et al. teach "thrombolytic agents", such as streptokinase, conjugated to "the fibrin binding domain of naturally occurring human fibronectin" (see column 20, lines 16-31). Vogel et al. further teach specific, effective fragments of human FN one of which fragments is an 18.5 kD fragment (see column 19, lines 58-64) corresponding to amino acids 1-154 of SEQ ID NO:16 (see column 16, lines 28-32). The Examiner notes that Applicants' residues 1-151 in Figure 6 correspond residues 4-154 of SEQ ID NO:16 of Vogel et al. (see Figure 2).

The Examiner notes that Vogel et al. do not teach recombinant technology to produce fusion proteins, and, thus, the specific embodiment (which must be clarified, see above) in Claim 1 of being a single polypeptide chain (fusion protein), is not anticipated by Vogel et al. Note the 103 rejection below.

18. Claim 32 is rejected under 35 U.S.C. 102(b) as being anticipated by Malke et al (IDS reference AE). The instant claims is drawn to a pharmaceutical compositions comprising a hybrid plasminogen activator and a stabilizer.

Malke et al. teach kringle-streptokinase proteins which, during purification, contain thioredoxin and DTT (see page 11, line 45) or glycine (see page 12, line 1). Since streptokinase is a plasminogen activator and kringles are not naturally associated with streptokinase, these kringle-streptokinase proteins are hybrid PG activators.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malke et al. (IDS reference AE) in view of Vogel et al. (this reference is related to IDS reference AF). The instant claims are drawn to fusion proteins comprising (1) streptokinase (SK) and (2) human fibronectin (FN) or fragments of human FN, which FN fragments comprise fibrin binding domains (FBDs) 1 and 2 or 4 and 5, and which fusion proteins activate PG after a 5-30 minute lag following exposure (Claim 3). The instant claims are also drawn to particular embodiments of fusion proteins, namely SK-FBD(1,2), SK-FBD(4,5), FBD(4,5)-SK (note N and C-terminus order) (Claim 2, see Figure 6, embodiments A-C).

Malke et al. teach "the synthesis of hybrid streptokinase with fibrin binding domains based on gene fusion technology" (see Abstract). While not specifically limiting useful fusion SK proteins to having FBDs bound to the N-terminus of SK (i.e. teaching that other fusions are not useful), Malke et al. only teach the fusion of FBDs to the N-terminus of SK. While Malke et al. teach fusion proteins comprising SK and fibrin binding domains, Malke et al. use FBDs from kringle regions of plasminogen, not FBDs from human FN.

Vogel et al. teach as described above. The conjugation teachings of Vogel et al. are not limited to conjugation via a particular location of SK to be useful.

Neither Vogel et al. nor Malke et al. teach a lag in PG activation by their SK/FBD(FN) conjugate or their FBD(PG)-SK fusion protein, respectively; however, said lag, which is an unclear limitation in Claim 1 and a clear limitation in Claim 3, is an inherent property of the fusion protein.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to produce the hybrid plasminogen activators (fusion protein) of the instant claims by combining the teachings of Malke et al. and Vogel et al. because Malke et al. teach generic fusion proteins comprising SK and fibrin binding domains and Vogel et al. teach a specific embodiment of fibrin binding domain, namely full length human FN and FBDs 1 and 2 of human FN. Moreover, such fusion proteins would have been obvious because Vogel et al. teach the combination of SK and full length human FN or fibrin binding domains 1 and 2 of human FN, although in conjugated, not fusion, form. Furthermore, this conjugation of Vogel et al. is not specific to a location on SK,

thus, in effect, teaching both N and C terminus conjugation. One would have been motivated to produce the conjugates of Vogel et al. via fusion protein technology (recombinant DNA technology) taught by Malke et al. to facilitate the production of the "conjugated" protein since a fusion protein is a specific embodiment of a conjugated protein, that is conjugated via an amide bond in the polypeptide chain. Moreover, both Malke et al. and Vogel et al. teach the usefulness of SK/FBD proteins, either as conjugates or fusions, as thrombolytic therapies (see Malke et al., page 2, lines 35-41 and Vogel et al., column 3, lines 19-46).

20. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malke et al. (IDS reference AE) in view of Rostagno et al. (IDS reference AV). The instant claims are drawn to fusion proteins comprising (1) streptokinase (SK) and (2) human fibronectin (FN) or fragments of human FN, which FN fragments comprise fibrin binding domains (FBDs) 4 and 5 (Claim 1). The instant claims are also drawn to a fusion protein with domains 4 and 5 fused to the N-terminus of SK (Claim 2, see Figure 1, embodiment C), and which fusion proteins activate PG after a 5-30 minute lag following exposure (Claim 3).

Malke et al. teach as described above. Malke et al. also teach, specifically, the fusion of FBD domains at the N-terminus of SK. Malke et al. does not teach the use of FBDs from human FN domains 4 and 5. Malke et al. also do not teach a lag in PG activation by their SK-FBD(PG) fusion protein.

Rostagno et al. teach the ability of domains 4 and 5 of human FN to bind fibrin (see page 31939, left column, top paragraph).

While neither Rostagno et al. nor Malke et al. teach a lag in PG activation by a fusion protein, said lag, which is an unclear limitation in Claim 1 and a clear limitation in Claim 3, is an inherent property of the fusion protein, which is obvious as described below.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to produce the hybrid plasminogen activator (fusion protein) of the instant claims by combining the teachings of Malke et al. and Rostagno et al. because Malke et al. teach generic fusion proteins comprising FBD-SK and Rostagno et al. teach a specific embodiment of fibrin binding domain with particularly good fibrin binding activity, namely FBDs 4 and 5 of human FN. One would have been motivated to produce the fusion protein of Malke et al. using the alternate fibrin binding domains of Rostagno et al. because said domains would be particularly useful in the fusion protein of Malke et al. by virtue of their ability to bind fibrin, as taught by Rostagno et al. Moreover, Malke et al. teach the usefulness of FBD-SK proteins in thrombolytic therapies (see Malke et al., page 2, lines 35-41).

Examiner's Comments

21. The Examiner indicates that the FBD(4,5)-SK-FBD(4,5) embodiment (i.e., domains 4 and 5 on both termini of SK) of the instant claims is neither anticipated nor ~~obviated~~ rendered obvious by the prior art.

2/23/01

Conclusion

22. No claims are allowed in the instant application for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Kathleen M. Kerr whose telephone number is (703) 305-1229. The Examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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